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IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICANT(S):	Kalle SAKSELA *et al.*		
APPLICATION NO.:	09/579,894	GROUP:	1627
FILED:	May 26, 2000	EXAMINER:	B. Celsa
FOR:	METHODS AND MATERIALS FOR GENERATING SH3 DOMAINS WITH TAILORED BINDING PROPERTIES		

DECLARATION SUBMITTED UNDER 37 C.F.R.§1.132

Honorable Commissioner of Patents
Washington, D.C. 20231

I, Dr. Chi-Hon LEE do hereby declare the following.

I am the first author on the article Lee *et al.* The EMBO J. 14:5006-5015 (1995), which the Examiner cites in the Office Action of May 6, 2002.

As such, I am qualified to discuss the present invention and the work that was done in Lee *et al.*

I am aware of the Examiner's interpretation of the Lee *et al.* reference.

I am happy to provide the following comments regarding his invention related to artificial SH3 domains with engineered binding properties (RRT-SH3 domains) and studies that we pursued and published together in mid-90's at the Rockefeller University.

The main goal of my PhD work at RU was to use X-ray crystallography to solve the 3D structure of a protein complex of HIV-1 Nef and the SH3 domain of the Hck tyrosine kinase. Because of difficulties in obtaining good crystals of Nef/Hck-SH3 complexes, we became interested in

examining why the highly related SH3 domain of Fyn (which was known to have biochemical properties favorable for crystallization) bound to Nef less well than Hck-SH3. Based on comparison of the amino acid sequences of Hck and Fyn, we decided to try to introduce Hck-like amino acids into the RT-loop region of Fyn-SH3 domain. Indeed, the resulting chimeric Fyn/Hck-SH3 showed Hck-like binding to Nef, and allowed us to solve the molecular structure of Nef in complex with an SH3 domain, which was published in 1996 as an article in the prestigious journal *Cell*.

Despite our success in creating a Fyn-SH3 with Hck-like binding to Nef by introducing Hck-like amino acid substitution(s) into the RT-loop of Fyn-SH3, the results from subsequent work carried out in prof. Saksela's laboratory in Finland came as a surprise to me. The overall success of the RRT-SH3 approach, and even less so the astonishing capacity of non-natural hexapeptide substitutions in place of the EAIHHE amino acid sequence of Hck-SH3 to generate SH3 domains with novel binding specificities and antibody-like affinities, could not be anticipated from our earlier results.

As the first author of the study published in 1995 in *The EMBO Journal* (Lee *et al.*, *EMBO J.* Vol 14, pages 5006-5015) I believe to be well-positioned to evaluate the impact of this paper on prof. Saksela's later work on RRT-SH3 domains, which in my mind undoubtedly was innovative and non-obvious to myself or anybody else familiar with this field in light of our 1995 *EMBO J.* publication.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge

that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Chi-Hon Lee — March 2, 2004

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